

Supplementary Online Content

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eFigure 1. Consort Diagram: Patient Sample Availability, Sample Quality and Follow-up Information of the Patients in the Study.

eFigure 2. Distributions of GC Scores by Arm, Pathologic Stage, and Gleason Score

eFigure 3. Cumulative Incidence Estimates of Distant Metastasis and Death From Prostate Cancer and Kaplan-Meier Estimates of Overall Survival by GC Risk Group

eFigure 4. Prognostic Performance of GC for All Endpoints in the Full Analytic Cohort and Each Arm

eTable 1. Demographic, Baseline Clinical and Genomic Characteristics in Different Patient Sample Groups

eTable 2. Univariable and Additional Multivariable Analyses of GC

eTable 3. Interaction Effect of Treatment Arm and GC

eTable 4. 12-Year Predicted Rates in Each Arm by GC Risk Group, Difference in Rate Between Arms and Bootstrapped 95% CI

eTable 5. Univariable and Multivariable Analyses of GC in the Early Salvage Cohort

eTable 6. Univariable and Multivariable Analyses of GC in the Placebo Arm

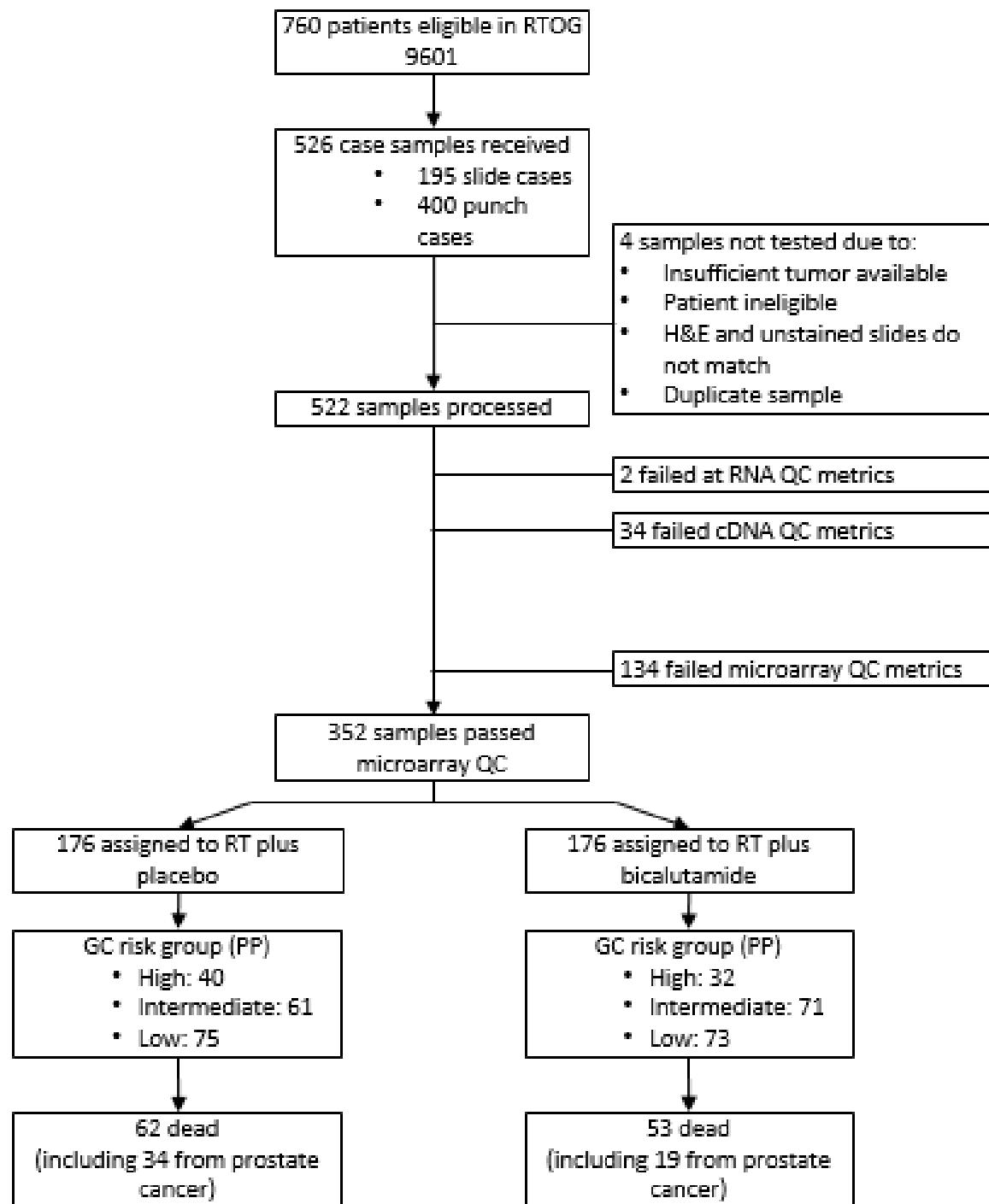
eTable 7. Model Comparison Across Cox PH With and Without Firth's Method and Fine-Gray

eMethods. Analysis Codes

This supplementary material has been provided by the authors to give readers additional information about their work.

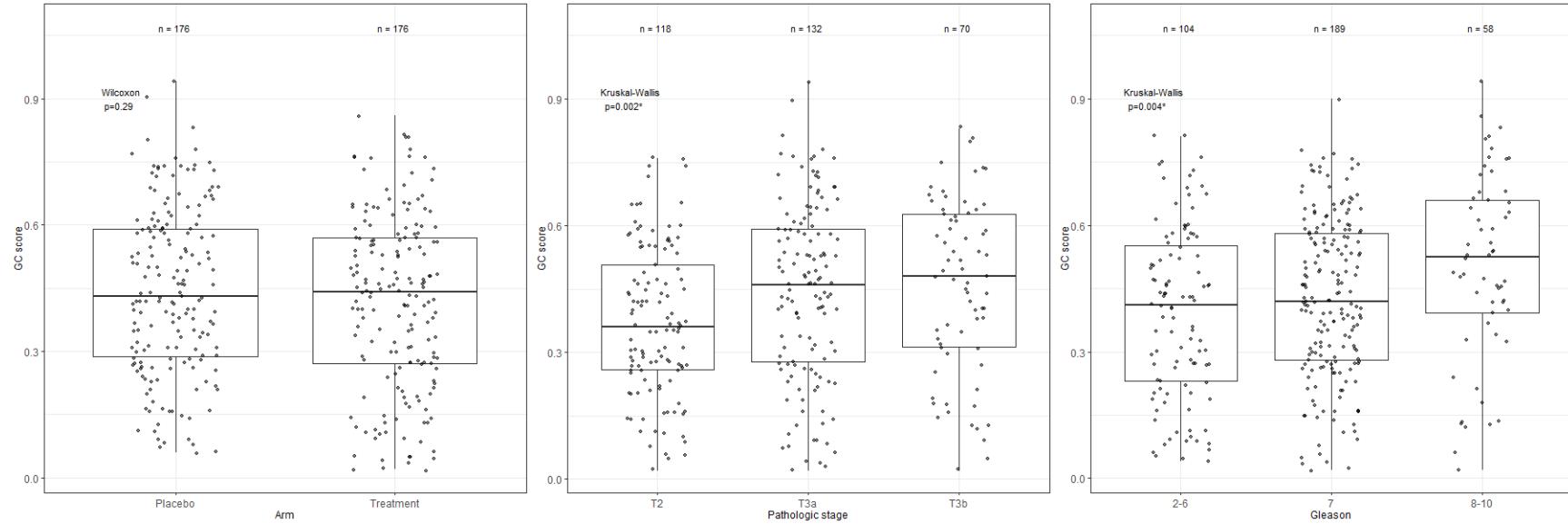
eFigure 1. Consort Diagram: Patient Sample Availability, Sample Quality and Follow-up Information of the Patients in the Study.

H&E = Hematoxylin and eosin staining; RP = radical prostatectomy; TURP = transurethral resection of the prostate; QC = quality control; RT = radiation therapy; PP = per-protocol.



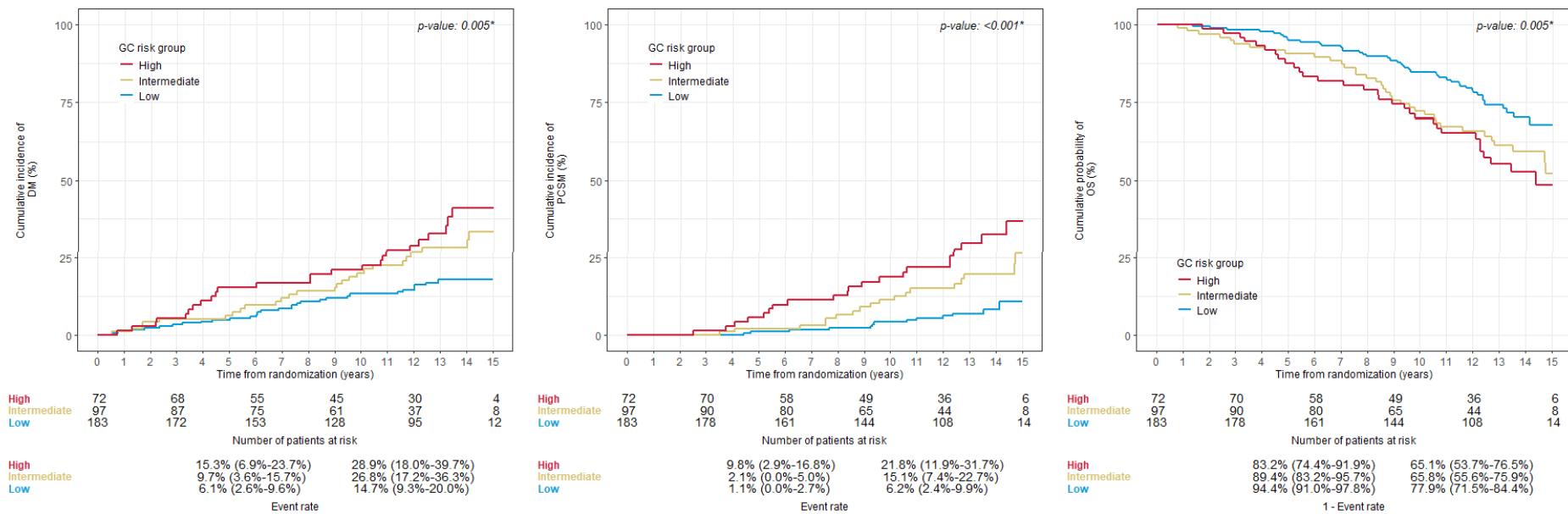
eFigure 2. Distributions of GC Scores by Arm, Pathologic Stage, and Gleason Score

GC score ranges from 0 to 1. The higher the score, the worse the prognosis. Pathologic stage T3 not otherwise specified were excluded.



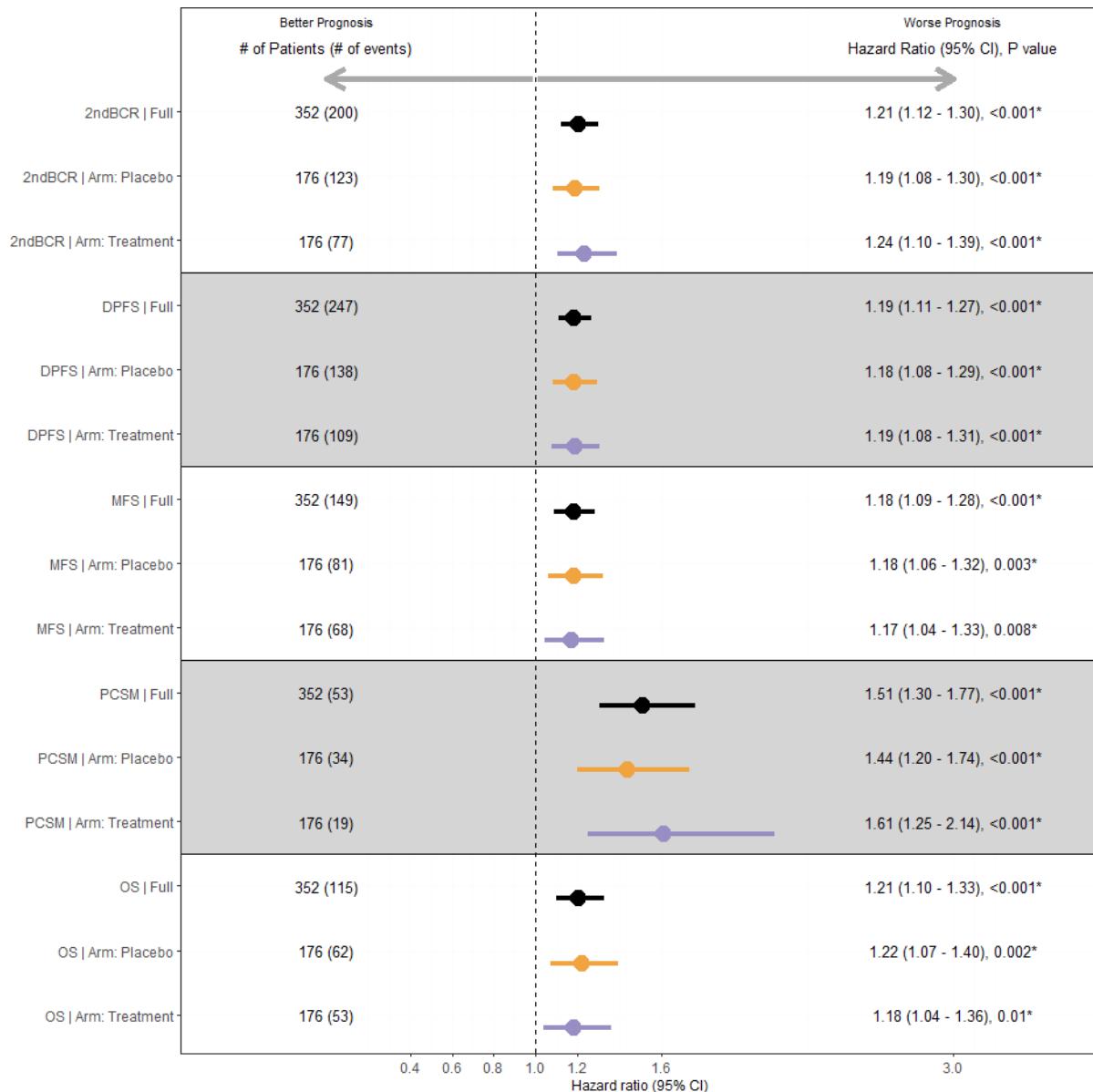
eFigure 3. Cumulative Incidence Estimates of Distant Metastasis and Death From Prostate Cancer and Kaplan-Meier Estimates of Overall Survival by GC Risk Group

All patients with samples passing assay quality control metrics. GC risk groups were categorized based on clinical use cut-points of 0.45 and 0.6. DM = distant metastasis; PCSM = death from prostate cancer; OS = overall survival.



eFigure 4. Prognostic Performance of GC for All Endpoints in the Full Analytic Cohort and Each Arm

The forest plot summarizes the subset univariable Cox regression results of GC continuous score (HR reported per 0.1-unit increase). 2ndBCR = secondary BCR post salvage radiation; DPFS = disease progression free survival; MFS = metastasis free survival; PCSM = death from prostate cancer; OS = overall survival.



eTable 1. Demographic, Baseline Clinical and Genomic Characteristics in Different Patient Sample Groups

The patients are grouped and compared based on their sample status: passed microarray QC (the cohort for analyses), failed microarray QC, failed in the wet lab prior to microarray, tissue not available. QC = quality control; PSA = prostate specific antigen; Q1 = first quartile; Q3 = third quartile; N/A = not applicable.

	Microarray QC Pass	Microarray QC Fail	RNA/cDNA Fail	Tissue not available	P-value
Total	352 (46.3)	134 (17.6)	36 (4.7)	238 (31.3)	
Assigned treatment					
Placebo	176 (50.0)	71 (53.0)	15 (41.7)	114 (47.9)	0.61
Treatment	176 (50.0)	63 (47.0)	21 (58.3)	124 (52.1)	
Age					
Median (Q1, Q3)	64.5 (60, 70)	64.5 (59, 69)	64.5 (57, 69.5)	65.0 (60.0 - 69.0)	0.828
≤49	4 (1.1)	1 (0.7)	2 (5.6)	3 (1.3)	
50-59	78 (22.2)	36 (26.9)	10 (27.8)	53 (22.3)	
60-69	181 (51.4)	65 (48.5)	15 (41.7)	125 (52.5)	0.51
70-79	85 (24.1)	30 (22.4)	9 (25.0)	57 (23.9)	
≥80	4 (1.1)	2 (1.5)	0 (0.0)	0 (0.0)	
Race					
White	314 (89.2)	118 (88.1)	30 (83.3)	206 (86.6)	0.64
Non-White	38 (10.8)	16 (11.9)	6 (16.7)	32 (13.4)	
Karnofsky performance status score					
80	4 (1.1)	3 (2.2)	0 (0.0)	2 (0.8)	
90	88 (25.0)	31 (23.1)	11 (30.6)	45 (18.9)	0.40
100	260 (73.9)	100 (74.6)	25 (69.4)	191 (80.3)	
Gleason score					
2-6	104 (29.5)	27 (20.1)	13 (36.1)	70 (29.4)	
7	189 (53.7)	82 (61.2)	13 (36.1)	129 (54.2)	
8-10	58 (16.5)	25 (18.7)	10 (27.8)	38 (16.0)	0.11
Unavailable	1 (0.3)	0 (0.0)	13 (36.1)	1 (0.4)	
T stage					
T2	118 (33.5)	40 (29.9)	15 (41.7)	75 (31.5)	
T3	234 (66.5)	94 (70.1)	21 (58.3)	163 (68.5)	0.56
Neoadjuvant hormone use					
Yes	23 (6.5)	6 (4.5)	9 (25.0)	11 (4.6)	<0.001
Positive surgical margins					
Yes	264 (75.0)	99 (73.9)	27 (75.0)	179 (75.2)	0.99
PSA nadir after surgery					
Median (Q1, Q3)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.15 (0.1, 0.2)	0.1 (0.1-0.3)	0.09
<0.5ng/ml	319 (90.6)	118 (88.1)	33 (91.7)	200 (84.0)	
≥0.5ng/ml	33 (9.4)	16 (11.9)	3 (8.3)	38 (16.0)	0.10
PSA level at trial entry					
Median (Q1, Q3)	0.7 (0.4, 1.1)	0.6 (0.4, 0.9)	0.6 (0.3, 0.9)	0.6 (0.4, 1.2)	0.29
<0.7ng/ml	175 (49.7)	73 (54.5)	22 (61.1)	135 (56.7)	
0.7-1.5ng/ml	119 (33.8)	43 (32.1)	11 (30.6)	64 (26.9)	0.43
>1.5-4.0ng/ml	58 (16.5)	18 (13.4)	3 (8.3)	39 (16.4)	
Follow-up (year)					
Median (Q1, Q3)	13 (11.7, 14.1)	13 (12, 13.9)	12.9 (11.5, 13.2)	13 (12, 14)	0.68

GC score

Median (Q1, Q3)

0.435 (0.28, 0.58) 0.6 (0.51, 0.68)

N/A

N/A

eTable 2. Univariable and Additional Multivariable Analyses of GC

One patient was dropped from the analyses due to missing Gleason information. The median age of the analytic cohort was 65. Race, Gleason, stage and nadir status were grouped according to the trial protocol. Other risk factors including age, race, Gleason, pathologic stage, PSA at trial entry, margin status and nadir status. CI = confidence interval; DM = distant metastasis; PCSM = death from prostate cancer; OS = overall survival; UVA = univariable analysis; MVA = multivariable analysis; PSA = prostate specific antigen.

Variable	Hazard ratio (95% CI) P-value		Hazard ratio (95% CI) P-value		Hazard ratio (95% CI) P-value		
	DM	PCSM	OS				
UVA GC	GC score	1.26 (1.12 - 1.41)	<0.001*	1.51 (1.30 - 1.77)	<0.001*	1.21 (1.10 - 1.33)	<0.001*
MVA: GC with arm and other risk factors	GC score	1.17 (1.05 - 1.32)	0.006*	1.39 (1.20 - 1.63)	<0.001*	1.17 (1.06 - 1.29)	0.002*
MVA: GC without arm and other risk factors	GC score	1.19 (1.06 - 1.33)	0.003*	1.38 (1.19 - 1.62)	<0.001*	1.17 (1.06 - 1.29)	0.001*
MVA: GC (commercial cut-point = 0.45) with arm and other risk factors	GC Intermediate-High vs. Low	1.74 (1.08 - 2.84)	0.02*	2.94 (1.57 - 5.81)	<0.001*	1.65 (1.12 - 2.45)	0.01*
	Treatment vs. Placebo	0.59 (0.37 - 0.91)	0.02*	0.50 (0.28 - 0.87)	0.01*	0.79 (0.54 - 1.14)	0.20
	Age 65+ vs. <65	1.31 (0.83 - 2.06)	0.24	1.53 (0.88 - 2.69)	0.13	1.98 (1.34 - 2.95)	<0.001*
	African American vs. non-African American	0.86 (0.28 - 2.07)	0.75	0.80 (0.16 - 2.53)	0.74	1.33 (0.56 - 2.74)	0.49
	Gleason 8-10 vs. 7-	2.20 (1.30 - 3.59)	0.004*	2.71 (1.49 - 4.75)	0.001*	1.91 (1.23 - 2.90)	0.005*
	T3 vs. T2	1.46 (0.84 - 2.64)	0.18	2.19 (1.07 - 5.03)	0.03*	1.28 (0.82 - 2.03)	0.28
	PSA level at trial entry	1.18 (0.89 - 1.50)	0.24	1.40 (1.03 - 1.84)	0.03*	1.09 (0.85 - 1.36)	0.48
	Margin status pos vs. neg	0.72 (0.44 - 1.18)	0.19	1.25 (0.68 - 2.42)	0.48	0.98 (0.64 - 1.54)	0.93
MVA: GC (per-protocol cut-point = 0.4) with arm and other risk factors	Non-nadir vs. nadir (<0.5ng/ml)	1.30 (0.61 - 2.50)	0.47	1.99 (0.87 - 4.07)	0.10	1.91 (1.09 - 3.19)	0.03*
	GC Intermediate-High vs. Low	1.88 (1.13 - 3.24)	0.01*	3.60 (1.76 - 8.31)	<0.001*	1.54 (1.03 - 2.34)	0.04*
	Treatment vs. Placebo	0.59 (0.37 - 0.92)	0.02*	0.52 (0.29 - 0.91)	0.020*	0.80 (0.55 - 1.15)	0.23
	Age 65+ vs. <65	1.32 (0.84 - 2.08)	0.23	1.56 (0.90 - 2.73)	0.11	1.98 (1.35 - 2.95)	<0.001*
	African American vs. non-African American	0.83 (0.27 - 1.98)	0.70	0.75 (0.15 - 2.30)	0.65	1.24 (0.53 - 2.53)	0.59
	Gleason 8-10 vs. 7-	2.21 (1.31 - 3.61)	0.004*	2.78 (1.53 - 4.89)	0.001*	1.97 (1.27 - 2.99)	0.003*
	T3 vs. T2	1.41 (0.81 - 2.56)	0.23	2.05 (1.00 - 4.72)	0.05	1.27 (0.81 - 2.01)	0.30

PSA level at trial entry	1.20 (0.91 - 1.53)	0.19	1.44 (1.06 - 1.89)	0.02*	1.11 (0.87 - 1.39)	0.38
Margin status pos vs. neg	0.71 (0.44 - 1.17)	0.17	1.24 (0.67 - 2.40)	0.51	0.96 (0.63 - 1.51)	0.87
Non-nadir vs. nadir (<0.5ng/ml)	1.31 (0.61 - 2.51)	0.46	2.14 (0.93 - 4.42)	0.07	1.91 (1.08 - 3.20)	0.03*

Hazard ratios of GC were per 0.1 unit increased. * asterisks indicate p-value <0.05.

eTable 3. Interaction Effect of Treatment Arm and GC.

CI = confidence interval; DM = distant metastasis; PCSM = death from prostate cancer; OS = overall survival; PSA = prostate specific antigen.

	Variable	Hazard ratio (95% CI) P-value		Hazard ratio (95% CI) P-value		Hazard ratio (95% CI) P-value	
		DM	PCSM	OS			
UVA	GC score	1.26 (1.12 - 1.41)	<0.001*	1.52 (1.30 - 1.77)	<0.001*	1.21 (1.10 - 1.33)	<0.001*
	GC Intermediate-High vs. Low	2.11 (1.34 - 3.33)	0.001*	3.63 (1.94 - 6.80)	<0.001*	1.82 (1.25 - 2.65)	0.002*
	Treatment vs. Placebo	0.60 (0.38 - 0.94)	0.03*	0.52 (0.30 - 0.92)	0.03*	0.80 (0.55 - 1.15)	0.23
Interaction model of GC with arm	GC score	1.24 (1.07 - 1.43)	0.004*	1.45 (1.21 - 1.75)	<0.001*	1.22 (1.07 - 1.39)	0.003*
	Treatment vs. Placebo	0.54 (0.15 - 1.92)	0.34	0.26 (0.04 - 1.95)	0.19	0.95 (0.35 - 2.59)	0.92
	GC in Treatment vs. Placebo	1.03 (0.82 - 1.30)	0.80	1.13 (0.81 - 1.57)	0.46	0.97 (0.80 - 1.17)	0.76
Interaction model of GC risk group with arm	GC Intermediate-High vs. Low	2.39 (1.33 - 4.31)	0.004*	3.54 (1.65 - 7.59)	0.001*	2.00 (1.20 - 3.33)	0.008*
	Treatment vs. Placebo	0.71 (0.34 - 1.48)	0.36	0.45 (0.14 - 1.46)	0.18	0.88 (0.49 - 1.58)	0.66
	GC Intermediate-High in Treatment vs. GC Low in Placebo	0.75 (0.30 - 1.91)	0.55	1.16 (0.30 - 4.42)	0.83	0.83 (0.39 - 1.76)	0.62

Hazard ratios of GC were per 0.1 unit increased. * asterisks indicate p-value <0.05.

eTable 4. 12-Year Predicted Rates in Each Arm by GC Risk Group, Difference in Rate Between Arms and Bootstrapped 95% CI

First half of the table for all patients in the full cohort; bottom half for early salvage patients only. The difference in rates was calculated from subtracting the predicted rate in the treatment arm from the placebo arm (GC risk group: Low = GC <0.45, Intermediate-High = GC 0.45-1). A positive difference in rates indicates that there is a treatment benefit from bicalutamide. The 95% confidence intervals were obtained using a bootstrapping procedure (see methods). DM = distant metastasis; PCSM = death from prostate cancer, OS = overall survival.

Cohort	GC risk group	12-year DM (%)			12-year PCSM (%)			12-year OS (%)		
		Rate in Placebo Arm	Rate in Treatment Arm	Difference in rate between arms (95% CI)	Rate in Placebo Arm	Rate in Treatment Arm	Difference in rate between arms (95% CI)	Rate in Placebo Arm	Rate in Treatment Arm	Difference in rate between arms (95% CI)
Full	Low	18.3	13.3	5.0 (-4.3, 14.7)	8.4	3.9	4.5 (-1.9, 11.7)	77.5	79.9	2.4 (-6.9, 13.0)
	Intermediate-High	38.4	22.7	15.7 (3.6, 28.6)	26.8	15.0	11.8 (1.5, 23.9)	60.1	69.0	8.9 (-2.1, 22.1)
Early Salvage	Low	12.8	12.3	0.4 (-12.7, 14.2)	2.5	1.5	1.0 (-4.6, 5.7)	86.4	78.6	-7.8 (-20.0, 5.9)
	Intermediate-High	32.9	21.7	11.2 (-10.0, 27.4)	17.7	9.3	8.4 (-3.1, 24.1)	69.7	74.2	4.6 (-14.2, 23.4)

eTable 5. Univariable and Multivariable Analyses of GC in the Early Salvage Cohort

Early salvage defined as <0.7ng/ml PSA at entry. CI = confidence interval; DM = distant metastasis; PCSM = death from prostate cancer; OS = overall survival; UVA = univariable analysis; MVA = multivariable analysis; PSA = prostate specific antigen.

Model	Variable	Hazard ratio (95% CI)		P-value	Hazard ratio (95% CI)		P-value	Hazard ratio (95% CI)		P-value
		DM	PCSM		OS					
UVA	GC score	1.31 (1.11 - 1.56)	0.002*		1.67 (1.30 - 2.18)	<0.001*		1.22 (1.06 - 1.41)	0.005*	
	Treatment vs. Placebo	0.77 (0.38 - 1.52)	0.45		0.60 (0.23 - 1.47)	0.27		1.16 (0.66 - 2.03)	0.61	
	Age	1.00 (0.95 - 1.06)	0.89		1.03 (0.96 - 1.11)	0.38		1.08 (1.03 - 1.13)	<0.001*	
	African American vs. non-African American	0.80 (0.09 - 3.00)	0.78		0.49 (0.00 - 3.58)	0.58		0.54 (0.06 - 2.01)	0.42	
	Gleason 8-10 vs. 7-	2.95 (1.32 - 6.12)	0.01*		5.40 (2.19 - 13.17)	<0.001*		2.51 (1.32 - 4.54)	0.006*	
	T3 vs. T2	2.00 (0.96 - 4.63)	0.07		2.85 (1.00 - 10.88)	0.05*		1.49 (0.83 - 2.84)	0.19	
	PSA level at trial entry	10.14 (0.76 - 142.59)	0.08		5.59 (0.16 - 214.09)	0.34		5.58 (0.65 - 49.49)	0.12	
	Positive surgical margins	0.41 (0.21 - 0.83)	0.01*		0.71 (0.29 - 1.95)	0.49		1.05 (0.57 - 2.07)	0.89	
	Non-nadir vs. nadir (<0.5ng/ml)	5.86 (0.05 - 44.06)	0.34		17.86 (0.13 - 167.34)	0.17		16.56 (1.82 - 67.00)	0.02*	
MVA	GC score	1.24 (1.05 - 1.48)	0.01*		1.45 (1.14 - 1.89)	0.002*		1.15 (0.99 - 1.35)	0.07	
	Treatment vs. Placebo	-	-		-	-		-	-	
	Age	-	-		-	-		1.08 (1.03 - 1.13)	<0.001*	
	African American vs. non-African American	-	-		-	-		-	-	
	Gleason 8-10 vs. 7-	2.23 (0.93 - 4.95)	0.07		3.01 (1.13 - 7.85)	0.03*		2.05 (1.02 - 3.93)	0.05*	
	T3 vs. T2	-	-		1.83 (0.62 - 7.14)	0.29		-	-	
	PSA level at trial entry	-	-		-	-		-	-	
	Positive surgical margins	0.40 (0.20 - 0.81)	0.01*		-	-		-	-	
	Non-nadir vs. nadir (<0.5ng/ml)	-	-		-	-		13.00 (1.34 - 61.50)	0.03*	

Hazard ratios of GC were per 0.1 unit increased. * asterisks indicate p-value <0.05.

eTable 6. Univariable and Multivariable Analyses of GC in the Placebo Arm

CI = confidence interval; DM = distant metastasis; PCSM = death from prostate cancer; OS = overall survival; UVA = univariable analysis; MVA = multivariable analysis; PSA = prostate specific antigen.

Model	Variable	Hazard ratio (95% CI)		P-value	Hazard ratio (95% CI)		P-value	Hazard ratio (95% CI)		P-value
		DM	PCSM		OS	OS		OS		
UVA	GC score	1.23 (1.07 - 1.42)	0.004*		1.44 (1.20 - 1.74)	<0.001*		1.22 (1.07 - 1.40)	0.002*	
	Age African American vs. non-African American	1.01 (0.97 - 1.06)	0.62		1.02 (0.97 - 1.08)	0.48		1.04 (1.00 - 1.08)	0.05*	
		1.00 (0.27 - 2.58)	1.00		1.12 (0.23 - 3.35)	0.87		1.41 (0.52 - 3.09)	0.47	
	Gleason 8-10 vs. 7-	2.89 (1.54 - 5.19)	0.001*		4.73 (2.38 - 9.26)	<0.001*		2.15 (1.19 - 3.71)	0.01*	
	T3 vs. T2	1.82 (0.97 - 3.69)	0.06		2.85 (1.24 - 7.94)	0.01*		1.42 (0.83 - 2.54)	0.22	
	PSA level at trial entry	1.41 (1.07 - 1.81)	0.02*		1.57 (1.14 - 2.08)	0.007*		1.26 (0.96 - 1.60)	0.09	
	Positive surgical margins	0.63 (0.35 - 1.16)	0.14		0.91 (0.44 - 2.01)	0.80		0.81 (0.48 - 1.43)	0.45	
	Non-nadir vs. nadir (<0.5ng/ml)	0.90 (0.25 - 2.31)	0.84		1.86 (0.60 - 4.53)	0.26		1.90 (0.85 - 3.71)	0.11	
MVA	GC score	1.17 (1.01 - 1.36)	0.04*		1.30 (1.08 - 1.57)	0.005*		1.19 (1.04 - 1.37)	0.01*	
	Age African American vs. non-African American	-			-			1.05 (1.00 - 1.09)	0.03*	
		-			-			-	-	
	Gleason 8-10 vs. 7-	2.49 (1.30 - 4.56)	0.007*		3.89 (1.92 - 7.76)	<0.001*		1.92 (1.04 - 3.38)	0.04*	
	T3 vs. T2	-			1.82 (0.77 - 5.15)	0.18		-	-	
	PSA level at trial entry	1.42 (1.07 - 1.84)	0.02*		1.60 (1.14 - 2.18)	0.007*		-	-	
	Positive surgical margins	-			-			-	-	
	Non-nadir vs. nadir (<0.5ng/ml)	-			-			-	-	

Hazard ratios of GC were per 0.1 unit increased. * asterisks indicate p-value <0.05.

eTable 7. Model Comparison Across Cox PH With and Without Firth's Method and Fine-Gray

PH = proportional hazards; CR = competing risks; CI = confidence interval; DM = distant metastasis; PCSM = death from prostate cancer; OS = overall survival; PSA = prostate specific antigen.

Model	Variable	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Subdistributional hazard ratio (95% CI)	P-value
		Cox PH (Firth's)		Cox PH (no Firth's)		Fine-Gray (OS as CR)	
DM	GC score	1.17 (1.05 - 1.32)	0.006*	1.18 (1.05 - 1.32)	0.006*	1.18 (1.05 - 1.33)	0.006*
	Treatment vs. Placebo	0.62 (0.39 - 0.97)	0.04*	0.62 (0.39 - 0.98)	0.04*	0.58 (0.37 - 0.92)	0.02*
	Age 65+ vs. <65	1.30 (0.83 - 2.06)	0.25	1.31 (0.83 - 2.06)	0.24	1.07 (0.68 - 1.68)	0.78
	African American vs. non-African American	0.88 (0.28 - 2.13)	0.80	0.80 (0.28 - 2.25)	0.67	0.64 (0.23 - 1.85)	0.41
	Gleason 8-10 vs. 7-	2.11 (1.24 - 3.47)	0.007*	2.08 (1.24 - 3.49)	0.005*	1.85 (1.09 - 3.11)	0.02*
	T3 vs. T2	1.42 (0.82 - 2.58)	0.22	1.44 (0.81 - 2.57)	0.22	1.36 (0.73 - 2.52)	0.33
	PSA level at trial entry	1.16 (0.88 - 1.49)	0.26	1.15 (0.89 - 1.50)	0.29	1.18 (0.93 - 1.50)	0.18
	Positive surgical margins	0.71 (0.44 - 1.16)	0.17	0.71 (0.43 - 1.16)	0.17	0.72 (0.43 - 1.19)	0.20
	Non-nadir vs. nadir (<0.5ng/ml)	1.31 (0.62 - 2.51)	0.46	1.26 (0.62 - 2.58)	0.52	1.12 (0.54 - 2.33)	0.77
PCSM	GC score	1.39 (1.20 - 1.63)	<0.001*	1.40 (1.20 - 1.63)	<0.001*	1.41 (1.21 - 1.63)	<0.001*
	Treatment vs. Placebo	0.53 (0.30 - 0.92)	0.03*	0.52 (0.29 - 0.92)	0.03*	0.50 (0.28 - 0.91)	0.02*
	Age 65+ vs. <65	1.52 (0.88 - 2.66)	0.14	1.53 (0.87 - 2.67)	0.14	1.39 (0.79 - 2.45)	0.25
	African American vs. non-African American	0.86 (0.17 - 2.73)	0.83	0.71 (0.16 - 3.08)	0.65	0.58 (0.15 - 2.24)	0.43
	Gleason 8-10 vs. 7-	2.53 (1.38 - 4.49)	0.003*	2.50 (1.38 - 4.52)	0.002*	2.33 (1.27 - 4.28)	0.006*
	T3 vs. T2	2.01 (0.97 - 4.62)	0.06	2.09 (0.95 - 4.62)	0.07	2.03 (0.86 - 4.78)	0.10
	PSA level at trial entry	1.37 (1.01 - 1.80)	0.04*	1.36 (1.01 - 1.81)	0.04*	1.36 (1.03 - 1.80)	0.03*
	Positive surgical margins	1.26 (0.68 - 2.44)	0.47	1.29 (0.68 - 2.44)	0.44	1.37 (0.72 - 2.62)	0.34
	Non-nadir vs. nadir (<0.5ng/ml)	2.10 (0.92 - 4.26)	0.07	2.02 (0.93 - 4.39)	0.08	1.63 (0.71 - 3.76)	0.25
OS	GC score	1.17 (1.06 - 1.29)	0.002*	1.17 (1.06 - 1.29)	0.002*		

Treatment vs. Placebo	0.82 (0.57 - 1.19)	0.29	0.82 (0.57 - 1.19)	0.30
Age 65+ vs. <65	1.95 (1.33 - 2.91)	<0.001*	1.96 (1.32 - 2.91)	<0.001*
African American vs. non-African American	1.35 (0.57 - 2.77)	0.47	1.28 (0.57 - 2.85)	0.55
Gleason 8-10 vs. 7-	1.87 (1.20 - 2.85)	0.007*	1.85 (1.20 - 2.86)	0.005*
T3 vs. T2	1.24 (0.79 - 1.97)	0.35	1.25 (0.79 - 1.97)	0.34
PSA level at trial entry	1.08 (0.84 - 1.35)	0.53	1.07 (0.85 - 1.35)	0.58
Positive surgical margins	0.98 (0.64 - 1.53)	0.92	0.99 (0.64 - 1.53)	0.95
Non-nadir vs. nadir (<0.5ng/ml)	1.98 (1.13 - 3.30)	0.02*	1.95 (1.14 - 3.35)	0.02*

Hazard ratios of GC were per 0.1 unit increased. * asterisks indicate p-value <0.05.

eMethods. Analysis Codes

```
library(tidyr)
library(broom)
library(survival)
library(coxphf)
library(glmnet)

## Loading required package: Matrix

##
## Attaching package: 'Matrix'

## The following objects are masked from 'package:tidyr':
## 
##     expand, pack, unpack

## Loaded glmnet 3.0-2

library(useful)

clin.vars.ana <- c("age_grp3", "race3", "pathgs_grp2", "pstage_grp",
                  "psa_study_entry", "sm", "psa_nadir_grp")

df <- dat.qcpass %>%
  select(esalv, met, met_time,
         os, os_time,
         pcsm, pcsm_time,
         decipher_1_dec, arm,
         one_of(clin.vars.ana)) %>%
  filter(complete.cases(.))
```

Excerpt of Analysis Codes

```
## log file ----
# UVA
coxphf(Surv(met_time, met) ~
  arm, data = dat.qcpass) %>%
  getDataFrame() %>%
  select(term:p.value)

##           term estimate      HR conf.low conf.high    p.value
## 1 armTreatment -0.5016818 0.6055115 0.3837229 0.9414113 0.02571255

coxphf(Surv(met_time, met) ~
  decipher_1_dec, data = dat.qcpass) %>%
  getDataFrame() %>%
  select(term:p.value)

##           term estimate      HR conf.low conf.high    p.value
## 1 decipher_1_dec 0.2283334 1.256504 1.123542 1.409392 5.360438e-05
```

```

# MVA
coxphf(Surv(met_time, met) ~
  decipher_1_dec + arm + age_grp3 + race3 + pathgs_grp2 + pstage_grp +
  psa_study_entry + sm + psa_nadir_grp, data = df) %>%
  getDataFrame() %>%
  select(term:p.value)

##          term  estimate      HR conf.low conf.high    p.value
## 1   decipher_1_dec  0.1611100 1.1748142 1.0475958 1.3224849 0.005629204
## 2   armTreatment -0.4757944 0.6213912 0.3910642 0.9717231 0.036893694
## 3   age_grp365+  0.2654314 1.3039934 0.8319659 2.0560089 0.247094806
## 4 race3African American -0.1267847 0.8809234 0.2829616 2.1258270 0.797693482
## 5   pathgs_grp28-10  0.7487450 2.1143448 1.2428208 3.4713347 0.006645982
## 6   pstage_grpT3  0.3505722 1.4198798 0.8157034 2.5763598 0.219826170
## 7   psa_study_entry  0.1526099 1.1648705 0.8847588 1.4899342 0.264367576
## 8           sm -0.3492053 0.7052483 0.4354017 1.1612046 0.166880186
## 9 psa_nadir_grp=0.5ng/mL  0.2725786 1.3133466 0.6150674 2.5107321 0.456404426

coxphf(Surv(pcsrm_time, pcsrm) ~
  decipher_1_dec + arm + age_grp3 + race3 + pathgs_grp2 + pstage_grp +
  psa_study_entry + sm + psa_nadir_grp, data = df) %>%
  getDataFrame() %>%
  select(term:p.value)

##          term  estimate      HR conf.low conf.high    p.value
## 1   decipher_1_dec  0.3313489 1.3928456 1.1979794 1.6345781 9.710956e-06
## 2   armTreatment -0.6381699 0.5282583 0.2950826 0.9188861 2.357992e-02
## 3   age_grp365+  0.4165478 1.5167165 0.8778200 2.6619161 1.358138e-01
## 4 race3African American -0.1454033 0.8646735 0.1719943 2.7340446 8.269117e-01
## 5   pathgs_grp28-10  0.9287810 2.5314214 1.3834789 4.4893083 3.167413e-03
## 6   pstage_grpT3  0.6957177 2.0051477 0.9694410 4.6223707 6.120586e-02
## 7   psa_study_entry  0.3151562 1.3704734 1.0132306 1.7993187 4.135194e-02
## 8           sm  0.2320718 1.2612103 0.6849636 2.4403208 4.645857e-01
## 9 psa_nadir_grp=0.5ng/mL  0.7436090 2.1035135 0.9244424 4.2641938 7.385515e-02

coxphf(Surv(os_time, os) ~
  decipher_1_dec + arm + age_grp3 + race3 + pathgs_grp2 + pstage_grp +
  psa_study_entry + sm + psa_nadir_grp, data = df) %>%
  getDataFrame() %>%
  select(term:p.value)

##          term  estimate      HR conf.low conf.high    p.value
## 1   decipher_1_dec  0.15442828 1.1669906 1.0596630 1.288165 0.0016153625
## 2   armTreatment -0.19749313 0.8207858 0.5658783 1.185912 0.2931070716
## 3   age_grp365+  0.66745386 1.9492679 1.3250679 2.907144 0.0006396791
## 4 race3African American  0.29953969 1.3492376 0.5694894 2.767823 0.4672386668
## 5   pathgs_grp28-10  0.62795178 1.8737688 1.1999189 2.848956 0.0065230037
## 6   pstage_grpT3  0.21373586 1.2382955 0.7944507 1.971440 0.3498668674
## 7   psa_study_entry  0.07595599 1.0789151 0.8441691 1.348013 0.5298029412
## 8           sm -0.02260819 0.9776455 0.6379996 1.528422 0.9190061342
## 9 psa_nadir_grp=0.5ng/mL  0.68480998 1.9833949 1.1281383 3.304821 0.0187662009

## Interaction
coxphf(Surv(met_time, met) ~
  decipher_1_dec*arm, data = dat.qcpass) %>%
  getDataFrame() %>%

```

```

select(term:p.value)

##           term estimate      HR conf.low conf.high
## 1 decipher_1_dec  0.2129026 1.2372642 1.0706512 1.429805
## 2 armTreatment -0.6172550 0.5394231 0.1517993 1.916855
## 3 decipher_1_dec:armTreatment  0.0298378 1.0302874 0.8156986 1.301329
##       p.value
## 1 0.003913448
## 2 0.340011055
## 3 0.802276155

## risk diff
cox.fit <-
  coxph(Surv(met_time, met) ~
    decipher_1_cat2*arm, data = dat.qcpass)

fit.dat <- expand.grid(trt = unique(dat.qcpass$arm),
                       sig =unique(dat.qcpass$decipher_1_cat2))
names(fit.dat) <- c("arm", "decipher_1_cat2")

## predict and pull inverse survival prob and CI from survfit
fit.predict <- survfit(cox.fit, newdata = fit.dat)
ix <- max(which(fit.predict$time <= 12))
fit.dat$rate <- 1 - fit.predict$surv[ix, ]
fit.dat %>%
  arrange(decipher_1_cat2, arm) %>%
  group_by(decipher_1_cat2) %>%
  mutate(diff = lag(rate) - rate,
        diff = ifelse(is.na(diff), lead(diff), diff)) %>%
  spread("arm", rate)

## # A tibble: 2 x 4
## # Groups: decipher_1_cat2 [2]
##   decipher_1_cat2     diff Placebo Treatment
##   <fct>            <dbl>   <dbl>     <dbl>
## 1 Low              0.0500   0.183    0.133
## 2 Intermediate-High 0.157   0.384    0.227

## Placebo subset
# UVA
coxphf(Surv(met_time, met) ~
  decipher_1_dec,
  data = dat.qcpass %>%
  filter(arm == "Placebo")) %>%
  getDataFrame() %>%
  select(term:p.value)

##           term estimate      HR conf.low conf.high      p.value
## 1 decipher_1_dec  0.2071217 1.230132 1.066273 1.423241 0.004440662

# MVA
df %>%
  group_by(arm) %>%
  do(getDataFrame(
    coxphf(Surv(met_time, met) ~

```

```

decipher_1_dec + pathgs_grp2 + psa_study_entry,
  data = .))) %>%
filter(arm == "Placebo") %>%
select(term:p.value)

## Adding missing grouping variables: 'arm'

## # A tibble: 3 x 7
## # Groups: arm [1]
##   arm    term      estimate HR conf.low conf.high p.value
##   <fct>  <fct>     <dbl> <dbl>    <dbl>    <dbl>    <dbl>
## 1 Placebo decipher_1_dec 0.157 1.17  1.01  1.36  0.0345
## 2 Placebo pathgs_grp2 0.913 2.49   1.30   4.56  0.00676
## 3 Placebo psa_study_entry 0.352 1.42   1.07   1.84  0.0177

## early Salvage subset
df %>%
  group_by(esalv) %>%
  do(getDataFrame(
    coxphf(Surv(met_time, met) ~
      decipher_1_dec + pathgs_grp2 + sm,
      data = .))) %>%
filter(esalv == "eSalv") %>%
select(term:p.value)

## Adding missing grouping variables: 'esalv'

## # A tibble: 3 x 7
## # Groups: esalv [1]
##   esalv term      estimate   HR conf.low conf.high p.value
##   <fct> <fct>     <dbl> <dbl>    <dbl>    <dbl>    <dbl>
## 1 eSalv decipher_1_dec 0.215 1.24   1.05   1.48  0.0127
## 2 eSalv pathgs_grp2 0.801 2.23   0.932  4.95  0.0703
## 3 eSalv sm          -0.926 0.396  0.198  0.807 0.0116

```